Journal of Surgical Oncology 63:249–258 (1997)

REVIEW

Screening for Colorectal Cancer

RICHARD L. NELSON, MD*
Department of Surgery, University of Illinois College of Medicine, Chicago, Illinois

INTRODUCTION

The purpose of screening asymptomatic individuals for colorectal cancer (CRC) is twofold. The first is to diminish mortality from this illness through early detection and possibly through secondary prevention. The second is to select a limited number of people who are to be examined by colonoscopy. Colonoscopy is the inevitable result of a positive screening test for several reasons. Direct visualization of the entire colorectum with the ability to obtain biopsy of discovered pathology makes this the definitive diagnostic tool. No elective operation upon the colorectum would be undertaken without a histologic diagnosis of disease and the careful elimination of synchronous lesions. Operation might even be avoided by the therapeutic ablation of smaller neoplasms.

Which is the most important goal of screening—to diminish mortality or to select people for colonoscopy? In a human and compassionate sense, clearly the first, for with it comes prolongation of life and good health. In a social, economic, or political sense, it is the latter. Although colonoscopy has been suggested as a screening strategy, universal colonoscopy is still considered too expensive and too dangerous, and therefore it must be rationed to those most likely to have positive findings.

In the colorectum there is a confusing stratification of interventions variously referred to as screening, surveillance, diagnostic evaluation, and therapeutic intervention. Definitions are not universally agreed upon, but, generally, screening might be defined as stratification of risk among apparently asymptomatic average risk individuals. Those with a positive screen are felt to be at increased risk for CRC and are then subjected to surveillance. This might include as well individuals with a history of CRC, polyps, ulcerative colitis, or a family member with CRC. The corollary not yet proven is that those with a negative screen have a substantial decrease in CRC risk (discussed later). Individuals who have symptoms of CRC or a positive surveillance test are then urgently subjected to diagnostic evaluation, that is, periodic examination is replaced by timely intervention for the subject who has become a patient. If the diagnostic test is positive, then therapy (surgery or otherwise) is undertaken. Implied in these definitions is that each level of intervention has its own unique test modality, presumably with cost and risk increasing at each ascending level. Yet, colonoscopy could be slotted into each. Why, then, treat them as being any different from each other? A look at past successful screening endeavors in other disease areas might help clarify or resolve this paradox (Table I).

PAST SCREENING

Disease screening of asymptomatic individuals might be undertaken if the disease has serious health consequences, if early diagnosis and therapy reduce the risk of those consequences, reducing health care costs. The test should be effective in making the diagnosis or stratifying risk, and neither the screening test nor what it leads to should be too expensive. Most importantly, the best screen is one that is likely to be used by those for whom it is intended. An example of an ineffective screen might be the examination of family members of patients with inflammatory bowel disease. Although the diseases are certainly serious and costly, there is no evidence that early intervention, especially in asymptomatic individuals, could alter the natural history of the illness. Screening of newborns for phenylketonuria (PKU) is, in contrast a paradigm that epitomizes the usefulness of screening because dietary intervention can prevent mental retardation and life-long institutionalization. The usefulness of PKU screening includes especially the last criterion, since screening is mandated and performed on all newborns.

Direct cost savings to society might be expected to arise from each screen in Table I either through decreased spread or severity of disease or avoidance of institutionalization, except for the last one (and possibly the applicants for insurance policies). In the case of the last, screening takes place at the end of life, when other

*Correspondence to: Richard Nelson, M.D., Department of Surgery, University of Illinois Hospital, 1740 West Taylor, Room 2204, M/C 957, Chicago, IL 60612. FAX: 312 996 2704.
Accepted 22 August 1996

TABLE I. Screening for Other Than Colorectal Cancer

Year	Subject	Diagnosis sought	Beneficiary of screen	Intervention
18th C	Prostitutes	STD[a]	Customers	Quarantine
1918, 1941	Draftees	Global fitness	Civilian population	Deferral
1940–70	Marriage license	Syphilis	Spouse	Penicillin
1996	Pregnant women	Diabetes, anemia	Infant	Specific therapy
1996	Insurance applicants	HIV,[b] diabetes, hypertension	Stockholders	Refusal or higher rate
1996	Employees	Tuberculosis	Fellow workers	Specific therapy or quarantine
1996	Blood donors	Hepatitis, HIV	Recipients	Discard blood
1996	Neonates	Phenylketonuria, cretinism	SUBJECTS	Specific therapy
1996	Boxers	HIV[b]	Opponents	Disqualification
1996	Everyone else	Cancer, heart disease	SUBJECTS	Diagnostic evaluation or therapy

[a]Sexually transmitted disease.
[b]Human immunodeficiency virus.

illnesses will inevitably follow, even if, for example, CRC is avoided or successfully treated. The goal of screening the elderly for CRC is improved quality and duration of life, with the social benefit perhaps being extension of productivity. A cost is incurred by the screen that is not balanced against a savings, therefore, but measured against what people, or their representatives, are willing to pay for the individual benefit. Current practice is to use the benchmark value of $40,000 per year of life saved as a socially acceptable value. This number arose from two sources. Renal dialysis costs about $45,000 per year and is paid by Medicare. Mammography screening for breast cancer costs about $37,000 per year of life saved by the screen. Through their reimbursement by Medicare, these two modalities have been determined to be worthwhile. This has not in the past assured, however, that any endeavor costing less than this will be approved for funding through federal or private agencies. CRC screening, which is still not covered by Medicare, is the best example. Effective screening modalities costing less than $15,000 per year of life saved are available for CRC [1].

If it is accepted that universal periodic colonoscopy is not to be recommended because of cost and risk of injury (this question is discussed further below), then it is necessary to use less costly and risky screening techniques as gates to colonoscopy. Each of the modalities listed in Table II is discussed in this context of cost, effectiveness, and risk and recommendations developed for optimal CRC screening.

TABLE II. Potential Colorectal Cancer Screening Tools*

Screening modality	Best detects	Most often done
Fecal occult blood	Cancer	Annually
Digital rectal examination	Cancer	Annually
Rigid proctoscopy	Neoplasia	
Flexible sigmoidoscopy	Neoplasia	3–10 yearly
Air contrast barium enema	Neoplasia	3–10 yearly
Colonoscopy	Neoplasia	3–10 yearly
Genetic screening	Cancer risk	One time
Ferritin	Polyps	One time
Symptom history	Cancer	Annually
Personal health history	Neoplasia	
Family health history	Cancer risk	One time
Personal demographics	Colorectal cancer subsite risk	One time

*(Not all currently recommended.)

FECAL OCCULT BLOOD TESTING

More has been written on the topic of fecal occult blood testing (FOBT) than on any other CRC screening technique. This volume of literature has been generated by an as yet unresolved confrontation between those who are committed to fecal occult blood testing and those who are convinced of its uselessness. Reported test accuracy results vary widely, with sensitivity for CRC varying from 30% to 92% and specificities from 90% to as high as 99% [1–3]. The higher numbers have been reported from research trials in which there was extensive patient and research personnel education, often incomplete ascertainment, and manipulation of test accuracy through rehydration of FOBT slides (Fig. 1).

More than half the time spent by this author in preparation of this report has been in the attempt to make sense of FOBT. To start with, it is difficult enough to remember what sensitivity and specificity individually mean. How study design variations might cause gross differences in these numbers added to the difficulty. To facilitate this discussion, presented below is a summary of definitions of measures of test accuracy. It is easiest to keep these definitions straight if the 2 × 2 grid, which forms the substance of all epidemiologic investigation, is kept in mind.

Sensitivity, Specificity, and Relative Risk

Sensitivity = % diseased with + test = a/a + c (Fig. 2). Specificity = % *not* diseased with − test = d/b + d. Positive predictive value = test + that are diseased = a/a + b. Negative predictive value = test − that are healthy = d/c + d. False positives = b/b + d. False negatives =

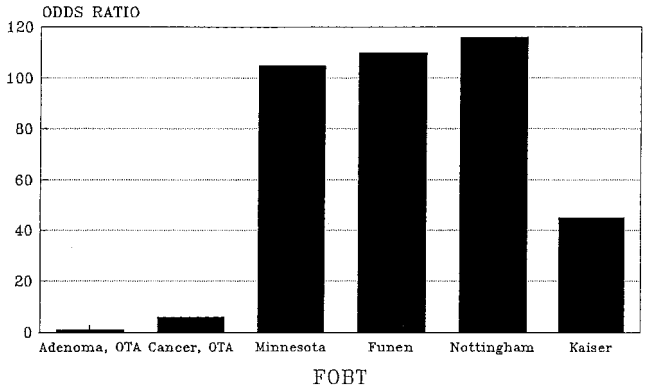

Fig. 1. Comparison of odds ratios for fecal occult blood test (FOBT) accuracy in diagnosing adenoma (column 1) and colorectal cancer (columns 2–6) in various reports [1,2]. The odds ratio for cancer approximates the relative risk. OTA = Office of Technology Assessment Review of Screening Reports.

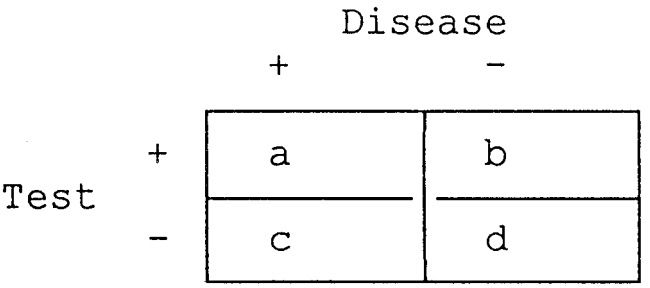

Fig. 2. The 2 × 2 table used to calculate test accuracy or risk association with a disease.

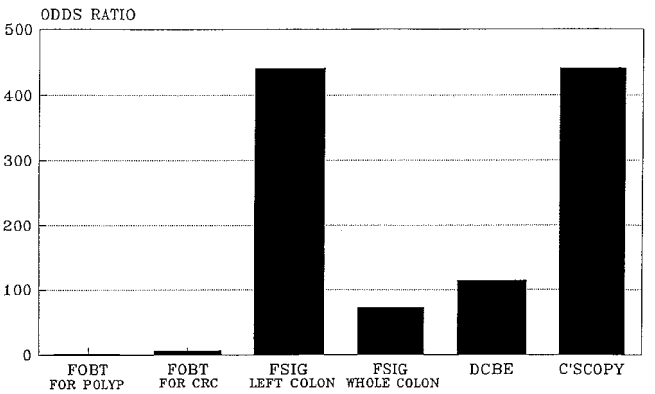

Fig. 3. Comparison of odds ratios of test accuracy in screening for colonic adenoma (column 1) and colorectal cancer (CRC) (columns 2–6) [1]. FOBT = fecal occult blood test, FSIG = fiberoptic flexible sigmoidoscopy, DCBE = air double contrast barium enema, C'SCOPY = colonoscopy.

c/a + c. Accuracy of the test = (a + d)/(a + b + c + d) = % tests that are correct. Specificity + false positives = 1. Sensitivity + false negatives = 1. Pretest prediction of patient disease status = age-specific population prevalence of the disease. After test, if (−) then d/c + d = negative predictive value, if (+) then, a/a + b = positive predictive value.

Sensitivity and specificity are characteristics of the test alone and are independent of population disease prevalence rates. Predictive values are more influenced by the prevalence of the disease. As each disease becomes more rare (e.g., looking for CRC in progressively younger age groups), the positive predictive value decreases greatly.

Each of the predictive values (+ & −) must exceed the prevalence of the illness for the test to be worthwhile. If the sensitivity (a/a + c) and specificity (d/d + b) of a test are known as well as the population prevalence of the illness (a + c)/(a + b + c + d), then each of the four values in the above grid can be identified, at least relative to each other, and the relative risk (RR) calculated, or simply the ratio of disease rate in test positive individuals (a/{a + b}) over disease rate in test negative individuals (c/{ c + d}). If a guess whether a subject has CRC, based upon the test result, is equal to the population prevalence at that subject's age, the RR = 1.0. If the guess is improved by two times, the RR = 2.0. In other words, the RR as a measure of test accuracy lets you know how a test alters your ability to tell if someone has a disease relative to the population prevalence with a single number that is easier to grasp than sensitivity and specificity. Because population prevalence figures play a key role in the calculation, this calculation, like the positive predictive value, is much more relevant to screening tests that are to be applied to an entire population than sensitivity and specificity. A more broadly applicable method of estimating the RR is by determining the odds ratio (OR = ad/bc), which approximates the RR for rare diseases, i.e., those diseases affecting <5% of the population, which, in the RR formula (RR = (ad + ac)/(ac + bc)), ac is assumed to be very small. The OR, like sensitivity and specificity, is unaffected by population prevalence [4] and is greater than the RR for common diseases such as adenoma. It also allows direct comparison of test modalities with a single number (Fig. 3).

FOBT Again

FOBT was first described as a screen for CRC in 1967 [5]. The author presented an extensive and insightful discussion of the potential and problems of FOBT and how it would relate to the other two screening tests then available, rigid proctosigmoidoscopy and barium enema. FOBT detects blood in the stool in small amounts when free hemoglobin is available to convert peroxide to oxygen and water. Intact red cells will not test positive, but other peroxidases will, such as myoglobin and horseradish. Very small amounts of blood, as are shed normally by the gastrointestinal tract every day, are usually not detected. That is, the test as it was initially conceived was intended to be somewhat insensitive to blood to avoid positive staining in individuals having normal gastroin-

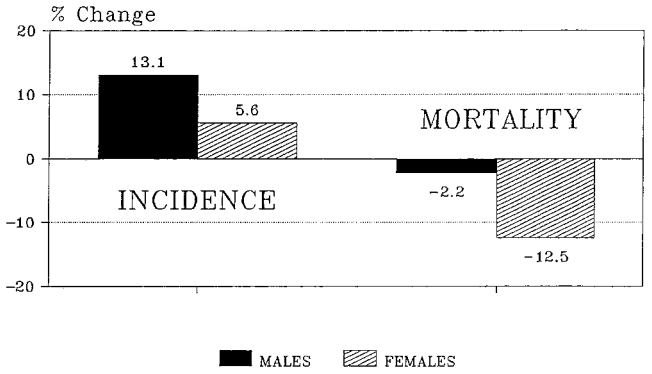

Fig. 4. SEER data on incidence and mortality from colorectal cancer from 1973 to 1986, showing a marked increase in incidence and decline in mortality. (Reproduced with permission of the publishers from Nelson RL, Persky V: The rise and fall of colorectal cancer. Dis Colon Rectum 1994;37:1175–1176.) SEER = Surveillance, Epidemiology and End Results; a cancer surveillance program of the National Cancer Institute.

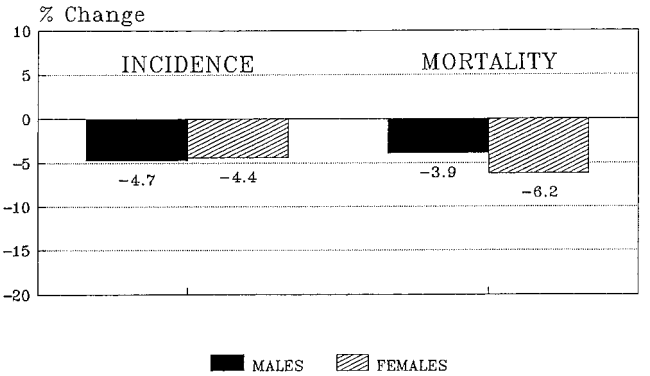

Fig. 5. SEER data on incidence and mortality from colorectal cancer from 1986–1990, showing a further decline in mortality, but for the first time a decline also in incidence of disease. (Reproduced with permission of the publishers from Nelson RL, Persky V: The rise and fall of colorectal cancer. Dis Colon Rectum 1994;37:1175–1176.) SEER = Surveillance, Epidemiology and End Results; a cancer surveillance program of the National Cancer Institute.

testinal blood loss. Subsequent attempts to increase the sensitivity of FOBT to blood, such as rehydration of Hemoccult II cards, Hemoccult Sensa, and HemeSelect must be viewed in this context [2,3].

The FOBT, of course, diagnoses nothing. It simply selects individuals for a diagnostic test. In its initial conception, that was barium enema. It is now colonoscopy. If the test succeeds, it is because those with a positive result are more likely to have colorectal neoplasia than those with negative FOBT cards. Yet 50% of patients with colorectal cancer have been reported to be FOBT negative and show no signs of anemia [6]. It is also hard to imagine why a benign adenoma, until it becomes quite large, should bleed. Because of *negative* FOBTs, 250 men were examined by colonoscopy and found to have a prevalence of cancer and polyps equal to those reported in FOBT positive individuals [7]. Those are individuals that would in the usual circumstance not have their tumors diagnosed until they were symptomatic and less curable.

In 1989, the United States Preventive Services Task Force (USPSTF) published its assessment of the efficacy of screening for CRC [8]. The endpoint used in judging efficacy was CRC mortality reduction in screened populations. In that publication, the rules of evidence for judging screening efficacy and a grading system for that evidence were outlined, varying from ''A'', a strategy proven efficacious and recommended for the particular group to which it was being applied, to ''C'', no evidence to support that strategy, to ''E'', the strategy has proven harmful and should be avoided. Sigmoidoscopy received a ''C'' grade for the general public >40 years of age. Fecal occult blood testing received a similar assessment, and more aggressive screening strategies, such as colonoscopy or computerized tomography, were not even mentioned in that article. They would probably have received ''D'' or ''E'' recommendations.

It seems extraordinary that strong evidence in support of CRC screening was not presented until 1992 [9], for sigmoidoscopy, FOBT in 1993 [2]. Many screening studies were published prior to 1992, but they were distracted from the real endpoint, mortality reduction, and focused instead on more accessible endpoints, principally assessment of the sensitivity of the screening modality. This rationale was accepted prior to the USPSTF because increasing sensitivity was felt to result in earlier detection, which should result in prolonged survival and increased likelihood of cure of primary disease. The inference of usefulness was made from this.

This USPSTF report was not well received by many individuals and organizations whose primary concern has been the reduction of cancer mortality. It was felt that no matter how indirect the evidence that screening was beneficial, that evidence was intuitively obvious and very compelling. This is best illustrated in a review of colorectal cancer mortality and incidence rates from SEER (Surveillance, Epidemiology and End Results; a cancer surveillance program of the National Cancer Institute) data (Fig. 4) [10]. It is frequently stated in publications concerning colorectal cancer that little has changed in colorectal cancer natural history or treatment in the last 50 years. Yet, in the first 13 years of the SEER program, there was a marked increase in colorectal cancer incidence, demonstrating a lack of success in primary or secondary prevention. However, mortality declined progressively over the same period. In the next 4 years, there was a reversal in the rising incidence of colorectal cancer, the first time this has been reported in any population, whereas mortality continued to decline (Fig. 5) [11]. The reasons for the change in incidence have not been

determined. One Scandinavian report suggested that increased survival was due exclusively to declining operative mortality [12]. If that were true in the United States, the tumor stages found at diagnosis should not have changed. In the SEER data, however, the rates of lower stages have been increasing and later stages progressively declined.

In 1993, mortality reduction associated with FOBT was reported [2,13,14] and shortly thereafter the USPSTF altered its recommendations concerning CRC screening to ''B'' [15], a critical step in getting screening paid for by private insurers. Medicare still does not reimburse for CRC screening.

The Minnesota FOBT screening study is frequently cited because it was the first to demonstrate mortality reduction in a randomized trial. But there were problems with that study that have been raised in correspondence. Only 46% of the study population complied with all the screens [16]. Although mortality was reduced in the annually screened group, it was not in a bi-annually screened group, a finding that seems inexplicable in the face of the 92% sensitivity for FOBT claimed by the authors [2]. Overall mortality was not decreased in the screened population, only CRC mortality. Could screening have costs manifested in different areas? Rehydration of the FOBT cards resulted in greater sensitivity, more false positives, and a 38% rate of colonoscopy in the screened population. It has been suggested that the mortality reduction largely could be explained by the high colonoscopy rate alone, regardless of how it was attained [17,18].

Most recently, more sensitive methods of detecting fecal occult blood have been compared to the original Hemoccult II in a trial that did not yet look at mortality reduction, but only sensitivity for CRC and adenoma >1 cm in diameter [3]. FOBT negative subjects were followed only for 2 years for cancer incidence and not subjected to colonoscopy. This incomplete ascertainment would have the effect of increasing both the sensitivity and specificity of the new tests. Sensitivity was improved for CRC detection with the new tests, but the cost of screening also increased substantially, and more extensive stool handling was needed by the subjects. Another report suggested repeat testing of FOBT positive individuals to increase accuracy, a strategy that will exclude many CRC patients from diagnostic workup and treatment [19].

Two more randomized studies of FOBT recently have been reported, each showing significant mortality reduction in screened populations. The reduction in mortality was less than in the Minnesota study (11% and 18%), but the percentage of the population subjected to colonoscopy was far less (1%), since rehydration was not used [20,21]. Can it be determined from these data that FOBT is the best screening method, or only that mortality reduction can be achieved by screening and more efficient screening methods should be sought?

GENETIC SCREENING

This screening method has received almost as much attention as FOBT in recent years, although in fact it has never been done. The fascination with genetic screening arises from several areas. First, familial clustering of colorectal cancer has been observed for many years, even excluding obvious familial syndromes such as familial adenomatous polyposis (FAP), hereditary nonpolyposis colon cancer (HNPCC), and inflammatory bowel disease (IBD). Second, the test would be only a blood draw and does not involve the collection and handling of stool or intubation of the rectum. Physicians know this will increase compliance with testing. Third, repeated testing is unnecessary, unlike the recommended annual FOBT. This would further increase compliance and perhaps decrease cost. Fourth, the recent discovery of specific genes associated with FAP and HNPCC may have established the feasibility of genetic screening [22].

So far, screening has occurred predominantly within kindreds known to have FAP or HNPCC. Some screening of CRC patients has also occurred. No prevalence studies of mutations at the FAP locus or any of the four HNPCC loci have been done in asymptomatic individuals unrelated to FAP of HNPCC patients. Even within FAP or HNPCC families, there has been no individual who has had a prophylactic colectomy based solely upon the results of identifying a mutation at one of the above loci [23]. Without population based data on the frequency and character of mutations at the loci associated with FAP and HNPCC, it is impossible to determine whether they are necessary or sufficient for CRC development in the general population.

There are several reasons to believe that the scientific basis of genetic screening is unsound [24]. The concept of a single base pair alteration being the cause of a common disease is attractive but unrealistic. Numerous mutations occur at the FAP and HNPCC loci, each probably with different biological effects and each modified by the complementary allele. As an illustration of this dilemma, sickle cell anemia is a hemoglobinopathy caused by a single base pair substitution. But there are hundreds of other hemoglobinopathies with widely varying clinical consequences. Are we to lump them all together, or develop separate screening, surveillance, and treatment pathways for each? Even 50 years after the discovery of the cause of sickle cell anemia, specific therapy for it has still not been developed [25]. For the colon, prophylactic colectomy is still the only available treatment for a positive screen [23]. Targeted primary prevention is often mentioned for CRC, but no specific strategy of proven efficacy short of colectomy, dietary or otherwise, exists. Even after colectomy in FAP and HNPCC, there is no

assurance that cancer might not develop in the rectum or in another organ.

The ethical basis of genetic screening also has been attacked, predominantly by individuals outside of the medical profession. Even if the consequences of carrying a ''disease gene'' were known—which they are not, people feel that the consequences of discovering the presence of that gene would be more negative than beneficial. Insurance would almost certainly be impossible to obtain, and already employers are looking at genetic data and family history to determine the fitness and therefore reliability of an employee. How will informed consent be obtained from a child for genetic screening [26,27]?

The cost of genetic screening also probably will be prohibitive. The tests needed are very specialized and despite the need to perform them only once, already exceed the lifetime cost of screening for CRC by established and efficacious methods such as FS [1,22]. Not included in current cost estimates are what might be done after a positive screen, although this is routinely included for cost estimates of other screening strategies. Lynch [22] has proposed annual colonoscopy for all individuals found to have mutations at any of the four mismatch repair loci associated with HNPCC beginning at age 25 years. If that adds up to 60 colonoscopies in 1% of the population, it is equivalent to doing colonoscopy on 60% of the population.

Explaining the results of genetic tests to individuals is difficult and time-consuming. The average practitioner is not qualified to do it. An army of genetic counselors would need to be trained and paid to accommodate for population-wide genetic screening. How many other diseases would be included in the screening protocol: breast cancer, diabetes, familial hypercholesterolemia? The cost of genetic screening will inevitably be huge.

FIBEROPTIC SIGMOIDOSCOPY

Fiberoptic sigmoidoscopy (FS) examines only the distal 60 cm of the colorectum. However, the coverage is adequate because >50% of CRC occurs in the distal colorectum, and a substantial number of individuals with cancer or adenomas proximal to the splenic flexure have neoplastic lesions distal to the splenic flexures as well [10,28,29]. For these individuals, total colonoscopy would follow FS and the proximal lesion discovered. It has been estimated that ~25% of all CRC would be missed in individuals screened by FS alone [29]. It also has been demonstrated that CRC subsite risk can be stratified by race and gender so that the yield of neoplasia found by FS could be increased by focusing FS screening on those individuals most likely to have distal disease (white males) and focusing total colon examinations by, for instance, barium enema on those individuals most likely to have proximal disease (African-American women) [28].

FS is the least controversial of all screening modalities. The fiberoptic sigmoidoscope has proven to be far superior to the rigid proctosigmoidoscope in finding distal colorectal neoplasia and as a result early concerns about the low yield of screening proctoscopy were laid to rest [30]. Nevertheless, the USPSTF in 1989, as noted above, gave only a type ''C'' recommendation to FS due to lack of proof of mortality reduction in screened populations. That demonstration was reported in 1992 in a case/control study in which the records of individuals who died of distal CRC and a matched control population were examined for the prevalence of prior proctosigmoidoscopy. A 70% decline in the risk of fatal distal CRC was associated with sigmoidoscopy done even at 10-year intervals [9]. As a result the USPSTF has altered its recommendation to type ''B'' [15]. FS has been demonstrated to be highly cost effective as a CRC screen [1] (see below), and efforts once again are being made to have FS screening reimbursed by Medicare.

BARIUM ENEMA

Air contrast barium enema (BE) is the forgotten screening modality. It is possible that BE's poor reputation lingers from the time when full column roentgenograms were routinely done. These films were most useful in finding stenotic ''apple core'' lesions, which were often advanced and incurable. Polyps and early cancers usually could not be detected. Most reviews on CRC screening never mention BE [31]. Correspondence by radiologists regarding such reviews reiterating the accuracy of BE for both cancer and large adenomas is practically ignored [32,33]. BE screening has not been shown to diminish mortality from CRC because the studies have not been done. Apparently, radiologists simply failed to get on the screening bandwagon as it passed through their towns. Statistical purists, many of whom are endoscopists, have therefore refused to consider BE as efficacious. Yet many studies have demonstrated BE to be equivalent to colonoscopy for the diagnosis of CRC and polyps >1 cm in size. BE images areas of the colon that are poorly visualized in colonoscopy, such as the flexures and sigmoid curve. The Office of Technology Assessment has determined that BE is as cost effective as FS in screening for CRC [1] (see below), and noted, its efficacy may exceed FS by focusing BE screening on those individuals most likely to have proximal disease [28].

COLONOSCOPY

Two factors prevent colonoscopy being applied to the whole population at risk: cost and morbidity risk [1,31]. Colonoscopy is still by far the most expensive CRC screening modality. Perforation of the colon also is more likely during colonoscopy than with other screening mo-

dalities, although the incidence of this complication is decreasing and those suffering perforation are in recent years more likely to be treated conservatively without surgery. However, the Minnesota FOBT trial in fact probably demonstrated that broadly applied colonoscopy more so than FOBT can decrease CRC mortality [2]. This mortality reduction might be accomplished either through early diagnosis of curable lesions, more accurate allocation to surveillance of those most at risk, individuals with adenomas, or cancer prevention through adenoma excision. Proponents of universal screening colonoscopy have constructed financial models that seem to make it cost competitive with other screening modalities [34]. However, the degree to which colonoscopy can prevent CRC is probably overstated and trauma costs underestimated in these models. Other cost estimates have not been so optimistic [1].

One intriguing idea that could make screening colonoscopy feasible is to do it once only at age 55 years. Only ~9% of CRC arises before that age [35]. Individuals <55 years old developing cancer would be diagnosed at the symptomatic stage of their disease, with considerable loss. However, adenomas are present in a large number of individuals by age 55. The prevalence of adenoma at age 55 years varies considerably from 11% to 35% [36]. Subjects found to have adenomas at colonoscopy would be offered regular surveillance. Those found to be adenoma-free would not be screened again. Up to 35% of the population would still be subjected to regular colonoscopy for polyp surveillance, but much of the cost of this might be compensated by the cost reduction of cancers prevented.

Before this proposal can be seriously considered, it is important to know what the CRC risk is in individuals who have no adenomas by age 55. For this proposal to have merit, this risk must be very low. Although certainly calculable from existing screening data, it appears never to have been published. This is a huge gap in the CRC screening literature. A similar proposal has been made for one-time universal FS at age 55 [35]. Although lives would be saved by this program, as they would in any CRC screen, the potential for loss of life through incomplete assessment is not adequately dealt with in the proposal. This seems needlessly frugal.

OTHER SCREENING MODALITIES

Digital rectal exam. The most common site of CRC in low risk populations is the rectum. Generations ago, when CRC had not reached the epidemic levels of risk that it has in the United States, it was taught that half of all CRC could be detected by the digital rectal examination (DRE). Today, it is probably <10% of CRC that can be so detected. There are many reasons to do DRE as part of a patient's physical assessment, but it has no place in population screening for CRC.

Rigid proctosigmoidoscopy. The rigid proctosigmoidoscopy is the usual instrument at a first office visit to investigate a patient with rectal bleeding or diarrhea. But the area of the colorectum that needs most careful screening, the sigmoid colon, is usually not reached by this instrument, especially in women and especially if prior to endoscopy they have had pelvic operations. FS, done with the same patient preparation and greater patient comfort, does visualize the sigmoid and often the descending colon as well. The rigid scope, therefore, has no role to play in CRC screening [30].

Family and symptom history. It would be very attractive to patients if screening could occur by mail in questionnaire form without having to take their clothes off. For instance, a family history would have to be obtained only once, or perhaps at protracted intervals to cover sibling illness. Symptom history is more problematic because of accuracy of reporting by subjects and compliance with the mail-in. As noted above, the goal of screening is to diagnose CRC or precancerous lesions before they become symptomatic. This is what has caused the decline in CRC mortality in the United States over the past 24 years. Presymptomatic screening also may be responsible for the recent decline in CRC incidence. Yet there are individuals with symptoms who defer seeing a physician who might be salvaged by such a questionnaire [37]. It seems that this screening technique must have been tried, but it has not appeared in the CRC screening literature.

Serum ferritin. Some people have stated a preference for a blood test rather than stool or colonic examination in screening. Genetic testing, as noted, is not broadly applicable beyond the rare dominant syndromes such as polyposis and is unlikely to become so [24,26]. Tumor-related serum antigens are likely to be elevated only in the face of incurable malignant disease [38]. It is most desirable, however, to find by screening those people carrying adenomas of the colorectum (Table II). They are the population most at risk for developing colorectal cancer, and risk may be reduced up to 70% if all adenomas are removed [39–41]. Elevated serum ferritin is roughly twice as accurate as FOBT in predicting the presence of colorectal adenoma [42]. Since ferritin elevation already has been demonstrated to be a cost-effective screening test for homozygous hereditary hemochromatosis, the added association with adenoma risk would further support population screening of serum ferritin.

COMPLIANCE AND ETHICAL CONSIDERATIONS

There are two reasons why such innocuous or beneficial endeavors as sigmoidoscopy and fecal occult blood testing should be subjected to rigorous assessment, beyond a purists devotion to scientific method. The first

Screening the "Worried Well"

STOP!
Are YOU Healthy?
Are YOU Sure?

Did you know that there is a
malignant disease called Screeningitis?

DON'T PANIC

There is a screening test available . . .
. . . and it is accurate . . .
. . . MOST of the time . . .

BUT the treatment is painful !! . . .

. . . AND HAS A LOW SUCCESS RATE !!!

Fig. 6. Is screening always beneficial? Only when the good outweighs the bad. (Reproduced with permission of D. Shickle and the publishers, from Shickle D, Chadwick R: The ethics of screening; is ''screeningitis'' an incurable disease? J Med Ethics 1994;20:12–18.)

relates to cost, since tests, no matter how simple, become very costly when applied to the whole population. Even more important, screening strategies are intended to be applied for the most part to individuals who are free of illness or symptoms and who, also for the most part, will derive no benefit from the screen. Since most colorectal cancers arise in individuals without risk factors such as colitis or polyposis, the whole normal population, most of whom will never get colorectal cancer, must be screened. False positive screens lead to more invasive diagnostic and therapeutic steps, further endangering healthy asymptomatic individuals. The benefit to the few with the disease should be demonstrable and clearly outweigh the risks to both those with the disease and those not to be benefited. The likelihood of benefit, which is frequently exaggerated to the public [27], should be understood both by the medical team and those who are to be screened. The risk that there might be personal costs of screening that are difficult to measure by traditional methods must be considered (Fig. 6) [43,44].

One study that attempts to address this problem is worth mentioning, both because of the ingenuity of its design and the way its results were interpreted [45]. Three groups—prospective jurors, medical ethicists, and experts in medical decision making—were presented with two scenarios and asked which they would recommend. Both scenarios related to colorectal cancer screening. A fixed amount of dollars were available for screening. In the first, a less expensive modality of screening could be used on an entire population, and 1,000 lives would be saved through screening. The second screening modality was more expensive but more effective. Therefore, only half the population could be screened, but in so doing, 1,100 lives would be saved. The less expensive (and less effective) screening modality was favored by 59% of the prospective jurors, 53% of the ethicists, and 41% of the decision makers, justifying their decision on the basis of equal access to screening for all, i.e., fairness. It seems regressive to the early days of screening to focus fairness on the act of screening rather than on the act of saving lives.

In any case, both the Health Interview Survey (HIS) [46] and the Behavioral Risk Factor Surveillance System (BRFSS) [47] have shown that the majority of Americans do not currently participate in CRC screening. Three modalities were assayed in the HIS: DRE, FOBT, and proctosigmoidoscopy (PS). Those most likely to be screened were white males >70 years, with rates increasing from 1987 to 1992 in most gender, race, and age groups. Similar results were reported in the BRFSS, which looked only at DRE and PS, although participation rates were slightly higher. A substantial number of these examinations were for the investigation of symptoms and therefore do not qualify as screening. The exception is the FOBT in the HIS. Participation rates for FOBT varied from 38–44% ever tested and 12–15% tested within the preceding year. Participation in FS screening has been shown to be increased if the likelihood of positive results is increased [48], but how is this to be done?

Cost Effectiveness

Recently, the Office of Technology Assessment of the U.S. Congress reviewed and reanalyzed the cost-effectiveness of colorectal cancer screening [1]. Six different screening strategies were used in their analysis: (1) annual FOBT, (2) FS every 3, 5, or 10 years, (3) BE every 3, 5, or 10 years, (4) colonoscopy every 3, 5, or 10 years, (5) FS every 5 years and FOBT annually, (6) BE every 5 years and FOBT annually.

Cost was determined by current Medicare reimbursement for each of the above procedures and various multiples thereof to cover different reimbursement situations. In addition, the cost of treating colorectal cancer of various stages was presented to calculate the cost savings of either earlier cancer detection in screening, or cancer prevention. Models were also calculated based on different lag times from polyp to cancer formation and different sensitivities of FOBT (Fig. 7).

Most screening modalities were found to fall below the $40,000 per year of life saved that is the benchmark for preventive strategies. Only colonoscopy at the highest cost estimates exceeded this value. The two most efficient strategies were five yearly FS ($13,216 per year of life saved) and BE ($13,844 per year of life saved), the

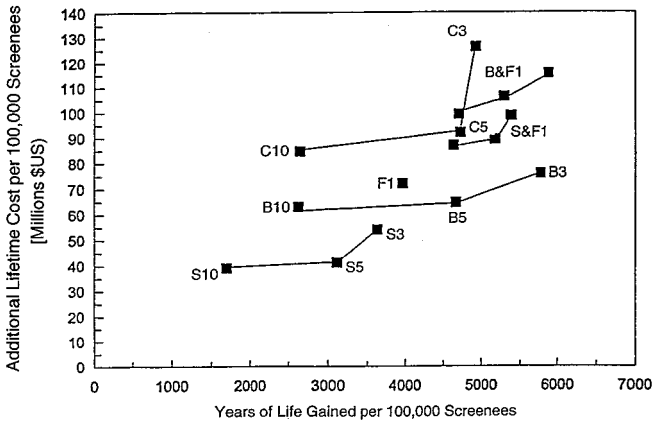

Fig. 7. Representative graph of models created by the Office of Technology Assessment of various screening strategies for colorectal cancer. The numbers following the letters indicate the frequency in years in which the tests would be performed. S = fiberoptic sigmoidoscopy; B = air double contrast barium enema; F = fecal occult blood testing; C = colonoscopy. The further down and to the right the strategy falls, the more cost effective it is [1].

latter being slightly more expensive but also more effective. The lifetime cost of screening for an individual age 50 in 1995 dollars using either of these strategies is $400–700, and the population at large would gain from this between 1 week and 1 month of additional life. Of course, the benefit would be concentrated in that 6% of the population at risk for cancer. The authors of this report conclude ''CRC screening in average risk adults at age 50 is a relatively good investment for society'' [1].

Problems

The problem that has generated so much attention concerning FOBT, of course, is that it is inaccurate. Too many people with CRC or adenomas will test negative and far too many individuals without neoplasia will test positive. The greater the effort to address the former problem, the greater the latter problem becomes [49]. The problem with colonoscopy is that it is too expensive and too dangerous, although these numbers are heading in the right direction. The trouble with BE is that nobody considers it seriously as a screening modality. It is plagued by the aura of being old-fashioned. The problem with DRE and the rigid proctosigmoidoscope are that they are too short. The problem with FS, which is true of all the above screening modalities, is that people do not want to handle their own feces or get diarrhea and have their rectums intubated. Screening compliance for all these ''bottom technologies'' in a voluntary system will be less than universal. The problem with genetic screening is that it may be based upon simplistic assumptions of what is contained within the FAP and HNPCC loci and how these genes work. It would create psychosocial burdens for the population being screened, and fully implemented, it would be expensive. The problem with waiting until subjects become patients with symptoms is that survival is poor because usually only the more advanced lesions cause symptoms of bleeding, obstruction, weight loss, or jaundice. It is most desirable, therefore, to find by screening those people carrying adenomas of the colorectum. They are the population most at risk for developing colorectal cancer, and risk may be reduced up to 70% if all adenomas are removed (Table II).

Recommendations

Too much effort seems to be spent on justifying FOBT when it compares so poorly with other modalities in predicting neoplasia (Fig. 3). DRE and rigid proctosigmoidoscopy are obsolete. FS or BE should be offered at 5-year intervals to asymptomatic individuals >50 years. Colonoscopy is being discussed as a one-time screen, but more needs to be known about individuals found not to have neoplasia at that screen. CRC costs ~$6,000,000,000 per year in the United States, over a third of this being for terminal care. Individuals with CRC have their lives shortened an average of 13.3 years [50]. Effective universal screening should be an urgent national priority.

REFERENCES

1. Wagner JL, Behney CJ, Tunis SR, Ching A: Cost-effectiveness of colorectal cancer screening in average risk adults. Office of Technology Assessment. United States Congress. BP-H-146. April 1995.
2. Mandel JS, Bond JH, Church TR, et al: Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365–1371.
3. Allison JE, Tekawa IS, Ransom LJ, Adrain AL: A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med 1996;334:155–159.
4. Wasserthiel-Smoller S: ''Biostatistics and epidemiology.'' New York: Springer Verlag, 1990.
5. Greegor DH: Diagnosis of large-bowel cancer in the asymptomatic patient. J Amer Med Assn 1967;201:123–125.
6. Kaster S, Buckley S, Haseman J: Colonoscopy and barium enema in the detection of colorectal cancer. (Abstract) Gastroint Endosc 1995;41:379.
7. Rex DK, Lehman GA, Hawes RH, Ulbright TM, Smith JJ: Screening colonoscopy in asymptomatic average-risk persons with negative fecal occult blood tests. Gastroenterology 1991;100:64–67.
8. US Preventive Services Task Force: Recommendations for sigmoidoscopic screening. J Amer Med Assn 1989;261:594–649.
9. Selby JV, Friedman GD, Quesenberry CP, Weiss NS: A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 1992;326:653–657.
10. Gloecker LA, Schatzkin A, Kaplan R: Colon and rectum. In Miller BA, Gloecker LA, Hankley BF, et al. (eds): ''SEER cancer statistics review 1973–1990.'' DHSS publ. No. 93-2789. 1993:VI.1–VI.10.
11. Nelson RL, Persky V: The rise and fall of colorectal cancer. Dis Colon Rectum 1994;37:1175–1176.
12. Enblad P, Adami HO, Bergstrom R, Glimelius B, Krusemo U, Pahlman L: Improved survival of patients with cancers of the colon and rectum. J Nat Canc Inst 1988;80:586–591.
13. Selby JV, Friedman GD, Quesenberry CP, Weiss NS: Effect of fecal occult blood testing on mortality from colorectal cancer: a case-control study. Ann Int Med 1993;118:1–6.
14. Wahrendorf J, Robra B, Wiebelt H, Oberhausen R, Weiland M, Dhom G: Effectiveness of colorectal cancer screening: results

from a population-based case-control evaluation in Saarland, Germany. Eur J Cancer Prev 1993;2:221–227.
15. US Preventive Services Task Force: ''Guide to clinical preventive services.'' 2nd ed. Baltimore: Williams & Wilkins, 1996.
16. Mandel JS, Church TR, Ederer F: Screening for colorectal cancer (Letter). N Engl J Med 1993;329:1353–1354.
17. Lang CA, Ransohoff DF: Fecal occult blood screening for colorectal cancer; is mortality reduced by chance selection for screening colonoscopy? J Amer Med Assn 1994;271:1011–1013.
18. Ahlquist D, Moertel CG, McGill DB: Screening for colorectal cancer (Letter). N Engl J Med 1993;329:1351.
19. Kewenter J, Engaras B, Haglind E, Jensen J: Value of retesting subjects with a positive Hemoccult in screening for colorectal cancer. Brit J Surg 1990;77:1349–1351.
20. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O: A randomized study of screening for colorectal cancer with fecal occult blood test in Funen Denmark. Lancet 1996;348:1467–1471.
21. Hardcastle J, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, James PD, Mangham CM: Randomized controlled trial of foecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472–1477.
22. Rossi SC, Srivastava S: National Cancer Institute workshop on genetic screening for colorectal cancer. J Nat Cancer Inst 1996; 88:331–339.
23. DeCosse JJ: Surgical prophylaxis of familial colon cancer: prevention of death from familial colon cancer. J Nat Cancer Inst Monograph 1995;17:31–32.
24. Hubbard R, Lewontin RC: Pitfalls of genetic screening. N Engl J Med 1996;334:1192–1193.
25. Hubbard R, Lewontin RC: Pitfalls of genetic testing (Letter). N Engl J Med 1996;335:1235–1257.
26. BW: Healthy fear of genetic tests. Int Herald Trib, 1996, May 25, p5.
27. Lee JL: Screening and informed consent. N Engl J Med 1993; 328:438–439.
28. Nelson RL, Dollear TM, Freels S, Persky V: The effect of age, gender and race on colorectal cancer subsite location. (submitted).
29. Dinning JP, Hixson LJ, Clark LC. Prevalence of distal colonic neoplasia associated with proximal colon cancers. Arch Int Med 1994;154:853–856.
30. Winan G, Bercy G, Banish J, Talbot TM, Overholt BF, McCallum RW: Superiority of the flexible to the rigid sigmoidoscope in routine proctosigmoidoscopy. N Engl J Med 1980;302:1011–1012.
31. Selby JV: How should we screen for colorectal cancer? Editorial. J Amer Med Assn 1993;269:1294–1296.
32. Ragozzino MW: Detection and surveillance of colorectal cancer (Letter). J Amer Med Assn 1990;263:374.
33. Clark RA, Halpert RD: Colorectal cancer screening (Letter). J Nat Cancer Inst 1991;83:1034.
34. Lieberman DA: Cost-effectiveness model for colon cancer screening. Gastroenterology 1995;109:1781–1790.
35. Atkin WS, Cuzick J, Northover JMA, Whyness DK: Prevention of colorectal cancer by once-only sigmoidoscopy. Lancet 1993;341: 736–740.
36. Berg JW: Epidemiology, pathology, and the importance of adenomas. In Steel G, Burt RW, Winawer SJ, Karr JP, (eds): ''Basic and clinical perspectives of colorectal polyps and cancer?'' New York: Liss, 1988, 14.
37. Nelson RL, Abcarian H, Davis FG, Persky V: Prevalence of benign anorectal disease in a randomly selected population. Dis Colon Rectum 1995;38:341–344.
38. Parikh SR, Attiyeh FF: Rationale for follow up strategies. In Cohen AM, Winawer SJ (eds): ''Cancer of the colon, rectum and anus.'' New York: McGraw-Hill, 1995, p718.
39. Murakami R, Tsukuma H, Kanamori S, Imanishi K, Otani T, Nakanishi K, Fujimoto I, Oshima A: Natural history of colorectal polyps and the effect of polypectomy on occurrence of subsequent cancer. Int J Cancer 1990;46:159–164.
40. Atkin WS, Morson BC, Cuzick J: Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992;326:658–662.
41. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, et al: Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med 1993;329:1977–1981.
42. Nelson RL: Elevation of serum ferritin is superior to fecal occult blood testing in the detection of colonic adenoma. Dis Colon Rectum 1996;39:1441–1442.
43. Perlman RP: Screening for colorectal cancer (Letter). N Engl J Med 1993;329:1352.
44. Shickle D, Chadwick R: The ethics of screening; is ''screeningitis'' an incurable disease? J Med Ethics 1994;20:12–18.
45. Ubel PA, DeKay ML, Baron J, Asch DA: Cost-effectiveness analysis in a setting of budget constraints—is it equitable? N Engl J Med 1996;334:1174–1177.
46. Trends in cancer screening. Morbid Mortal Weekly Rpt 1996;45: 57–61.
47. Screening for colorectal cancer—United States, 1992–1993, and new guidelines. Morb & Mort Weekly Rpt 1996;45:107–110.
48. McCarthy BD, Moskowitz MA: Screening flexible sigmoidoscopy; patient attitudes and compliance. J Gen Int Med 1993;8:120–125.
49. Ransohoff DF, Lang CA: Improving the fecal occult blood test (Letter). N Engl J Med 1996;334:1607.
50. Stat Bite: Average years of life lost from cancer. J Nat Cancer Inst 1995;87:956.